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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/807,506	02/27/1997	VICTOR SMIT	8524/71226	5096
42798	7590	01/23/2008		
FITCH, EVEN, TABIN & FLANNERY P. O. BOX 18415 WASHINGTON, DC 20036			EXAMINER BOESEN, AGNIESZKA	
			ART UNIT	PAPER NUMBER
			1648	
			MAIL DATE	DELIVERY MODE
			01/23/2008	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 08/807,506	<b>Applicant(s)</b> SMIT ET AL.	
	<b>Examiner</b> Agnieszka Boesen	<b>Art Unit</b> 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 94-111, 133 and 136-141 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 94-111, 133 and 136-141 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/14/2007</u> | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The Amendment filed November 14, 2007 in response to the Office Action of May 14, 2007 is acknowledged and has been entered. Claims 94-111, 133, 136-141 are pending and under examination.

#### ***Information Disclosure Statement***

The Information Disclosure Statement received November 14, 2007 been considered.

#### ***Claim Rejections - 35 USC § 112***

Rejection of claim 110 for lack of sufficient antecedent basis for the “substrate” is **withdrawn** in view of Applicant’s amendment.

Rejection of claims 94-111, 133, 136-141 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of Applicant’s amendment and arguments.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of claims 94-100, 104-106, 109, 133, 136, 137, and 140 under 35

U.S.C. 102(b) as being anticipated by Witkowska et al. (Hemoglobin, 1993, Vol. 17, p. 227-242)

**is withdrawn** in view of Applicant's arguments.

Rejection of claims 94-100, 106, 109, and 138 under 35 U.S.C. 102(b) as being anticipated by Knepper et al. (Biochemistry, 1992, Vol. 31, p. 11651-11659) **is withdrawn** in view of Applicant's arguments.

Rejection of claims 94-100, 106, and 109 under 35 U.S.C. 102(b) as being anticipated by Arcone et al. (European Journal of Biochemistry, 1991, Vol. 198, p. 541-547) **is withdrawn** in view of Applicant's arguments.

Rejection of claims 94-100, 106, and 109 are rejected under 35 U.S.C. 102(e) as being anticipated by Woods (US Patent 5,658,739) **is withdrawn** in view of Applicant's arguments.

Rejection of claims 94-100, 106, 109, and 138 under 35 U.S.C. 102(e) as being anticipated by Braford-Goldberg et al. (US Patent 5,501,962) **is withdrawn** in view of Applicant's arguments.

Rejection of claims 101-103 under 35 U.S.C. 103(a) 138 as being unpatentable over Knepper et al. (Biochemistry, 1992, Vol. 31, p. 11651-11659); Arcone et al. (European Journal of Biochemistry, 1991, Vol. 198, p. 541-547); Woods (US Patent 5,658,739); and Braford-Goldberg et al. (US Patent 5,501,962) as applied to claims 94-100, 106, 109, and 138 and further in view of Weber et al. (US Patent 5,710,252) and Rosnack et al. (Rapid Communication in Mass Spectrometry, 1992, Vol. 6, p. 637-640) **is withdrawn** in view of Applicant's arguments.

*New Rejection in view of newly found prior art and a reference submitted in IDS of 11/14/2007.*

**Claims 94-103, 106, 107, 109, 110, 111, 137-141 are rejected under 35 U.S.C. 102(b) as being anticipated or in the alternative under 35 U.S.C. 103(a) as being obvious over Smit et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007).**

Smit disclose a method of structure function analysis using mass spectrometry to monitor chemical modifications of zinc binding domain of IL-3, comprising gradual chemical modification of IL-3, monitoring the modification reaction, protease treatment, mass spectrometry, and assaying biological activity of the modified product (see the entire document). Smit discloses chemical modification of IL-3 amino acid residues His<sup>26</sup>, Lys<sup>28</sup>, His<sup>95</sup>, His<sup>98</sup>, and Lys<sup>10</sup> wherein protein digestion is performed using endoproteases Endo Glu and Endo Lys C and exoproteases carboxypeptidase Y (see page 859, Materials and Methods, and Figure 1). Smit discloses that chemical modifications of IL-3 result in loss of IL-3 binding zinc. Smit does not expressly disclose that chemical modifications of IL-3 result in enhanced stability, suppressed antigenicity, acquired antagonistic activity, or cell inhibitory activity. However it would have been obvious that the loss of IL-3 capability to bind zinc would result in an antagonistic activity of IL-3 because Smit discloses that zinc binding activity of IL-3 is involved in phosphorylation of IL-3 receptor. Thus an unmodified IL-3 ligand that is an agonist (receptor stimulator) when modified would be expected to become an IL-3 receptor antagonist (blocking receptor function and cascade of cellular events following receptor activation) as a results of the loss of its agonist

activity due to inability to bind zinc. Thus the skilled artisan would have expected that loss of zinc binding activity of IL-3 will result in acquired antagonistic activity as presently claimed. With regard to claim 139, it is noted that it is expected that the modified IL-3 disclosed by Smit, would have the properties to inhibit native IL-3 as require by the claims, absent any evidence on the contrary. Thus the present claims are anticipated/ obvious in view of Smit.

**Claims 94-100, 104-109, 133, 136, 137, 138, 140 and 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smit et al. (Electrophoresis, 1994, Vol. 15, p. 251-254) in view of Smit et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) and Builder et al (US Patent 4,511,502).**

Smit teaches mild and sensitive electrophoresis method and circular dichroism spectroscopy (which is a type of mass spectroscopy) to monitor chemical modifications of human interleukin-3 (see the entire document). Smit discloses gradual chemical modification of IL-3 by alkylation with acetic anhydride and proteases under pH of between 5.7 and 7.0 and in the presence of phosphate buffer (see pages 251 and 252). Smit discloses that chemical modifications of IL-3 result in conformational changes of IL-3 resulting in shift in electrophoretic mobility (see page 253). Smit does not expressly disclose that the conformational changes in IL-3 due to chemical modifications result in enhanced biological activity, enhanced stability, acquired antagonistic or inhibitory activity. Smit does not expressly disclose step e) of the present method: "assaying biological activity of the modified product".

However it would have been obvious that Smit's chemical modifications of IL-3 would result in a change of IL-3 function, wherein the change is an acquired antagonistic or inhibitory

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activity of IL-3, because Smit (1992) disclose that chemical modification of IL-3 results in inability of IL-3 to bind zinc and that zinc binding activity of IL-3 is involved in phosphorylation of IL-3 receptor. Thus an unmodified IL-3 ligand, an agonist (receptor stimulator) when modified would be expected to become an IL-3 receptor antagonist (blocking receptor function and cascade of cellular events following receptor activation) as a results of the loss of its agonist activity due to inability to bind zinc.

The skilled artisan would immediately envisage assaying biological activity of the chemically modified IL-3 because the purpose of IL-3 modification is to alter its biological activity as evidenced by Smit (1992). Thus it would have been obvious to assay the biological activity of chemically modified IL-3 because Smit (1992) teaches that chemical modifications of IL-3 result in loss of IL-3 to bins zinc which affect IL-3 function.

With regard to claim 136, it would have been obvious to use urea and EDTA in the method of Smit (1994) because as evidenced by Builder, urea and EDTA are commonly used chelating agents to prevent protease degradation and precipitation of the protein. EDTA is commonly used as a chelating agent and urea is added to maintain protein solubility. In the present case, the skilled artisan would have been motivated to maintain the stability of the IL-3 protein while performing chemical modifications. The skilled artisan would have been motivated to prevent IL-3 from precipitating from the solution by adding urea.

Thus the present invention would have been *prima facie* obvious to the person skilled in the art at the time when the invention was made.

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***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035.

The examiner can normally be reached on 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

*AB*

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 1-15-2008  
Primary Examiner, TC1600